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MINTZ, LEVIN, COHN, FERRIS, GLOVSKY
AND POPEO, P.C.
ONE FINANCIAL CENTER
BOSTON, MA 02111

| EXAMINER | |
|---|---|
| LEAVITT, MARIA GOMEZ | |
| ART UNIT | PAPER NUMBER |
| 1633 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/774,843 | PELED ET AL. | |
| | Examiner | Art Unit | |
| | Maria Leavitt | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *06-25-2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *401-414,416-419 and 421-463* is/are pending in the application.

4a) Of the above claim(s) *402-410,413,426-433,435 and 439-495* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *401,411,412,414-425,434,436-438,460 and 462* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

*Detailed Action*

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Status of claims. Claims **401-414, 416-419, 421-463** are currently pending. Claims **402-410, 413, 426-433, 435, 439-459, 461 and 463** have been withdrawn as being directed to non-elected inventions or species as stated at page 2 of the office action filed on 02-01-2007, pursuant to 37 CFR1.14(b), there being no allowable generic or linking claim. Claims 401, 411, 412, 421, 423, 462, and 463 have been amended and claims **415 and 420** have been canceled by Applicants' amendment filed on 06-25-2007.

3. The examiner notices that claims **425, 434 and 436-438** were inadvertently marked as withdrawn in the Office Action Summary PTOL-326 Form. However, these claims were not withdrawn as it is reflected in the examination and rejection of claims 425, 434 and 436-438 under 35 USC § 112 – first paragraph-enablement- in the office action filed on 02-01-2007. Claims 425, 434 and 436-438 read on the elected invention, e.g., a method of *ex vivo* expansion of stem cells involving an agent or culture condition with nicotinamide or a nicotinamide analog such as benzamide.

4. The examiner also notices that Applicants have wrongly stated at page 18 of Remarks that claims 402-410, 413, **425-259 and 461** are withdrawn and not 402-410, 413, **426-433, 435, 439-495, 461 and 463.**

5. Therefore claims **401, 411, 412, 414, 416-419, 421-425, 434, 436-438, 460, and 462** are currently being examined to which the following grounds of rejection are applicable.

***Withdrawn rejections in response to Applicant arguments or amendments***

***Claim Rejections - 35 USC § 102(e)***

In view of applicant amendment of claim 401 to recite " in the presence of a least 0.1 mM of exogenously added nicotinamide, nicotinamide analog" rejection of claims 401, 411-412, 414-418, 420-424 and 462 under 35 U.S.C. 102(e) as being anticipated by Brown R (US Publication No. 2002/0159984, Date of Publication October 31, 2002) has been withdrawn. Brown R teaches physiological concentration of nicotinamide of 4mg/L, which correspond to a molarity of 0.033 mM and thus Brown does not anticipate concentrations of "at least 0.1 mM".

***Claim Rejections - 35 USC § 112 – first paragraph-enablement***

In view of applicant arguments stating that an *ex vivo* expanded population of hematopoietic cells comprising CD34+ cells was known in the art, rejection of claim 460 under 35 USC § 112 – enablement has been withdrawn.

***Remaining rejections in response to Applicant arguments or amendments***

***Claim Rejections - 35 USC § 112 – first paragraph-enablement***

Claim 401, 411-412, 414-425, 434, 436-438, and 462 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of expanding an *ex vivo* population of $CD34^+$ and $CD34^+CD38^-$ hematopoietic stem cell in culture, while at the same time inhibiting differentiation of the said cells; said method comprising:

(a) providing hematopoietic CD34+ cells that are not enriched prior to culturing , culturing said CD34+ cell cultures *ex vivo* under conditions allowing the proliferation; said conditions for *ex-vivo* cell proliferation comprises providing a combination of cytokines selected from the group consisting of stem cell factor (SCF), TPO, FLt3, IL-6 and IL-3, and

(b) culturing said CD34+ cell cultures in presence of concentrations of 1-10 mM of exogenously added nicotinamide for up to three weeks culture period ;

thereby expanding the population of said hematopoietic stem cell while inhibiting the differentiation of said CD34+ cell cultures *ex vivo* in culture medium.

does not reasonably provide enablement for expanding any other population of stem cell or culturing said hematopoietic CD34+ cells in presence of any other condition for proliferation while at the same time inhibiting differentiation of the said cells.

***Response to Applicant Arguments as they apply to rejection of claims 401, 411-412, 414-425, 434, 436-438, 460, and 462 under - 35 USC § 112 – first paragraph-enablement***

On page 19 of Remarks, Applicants state that to expedite prosecution "independent claims 401 (from which claims 414, 416-419, 421-424 depend), 411, 412 and 463 are amended to require that the stem cells are "hematopoietic stern cells" and require that the hematopoietic stem cells are cultured or propagated in the presence of "at least 0.1 mM of exogenously added nicotinamide, nicotinamide analog or nicotinamide derivative". As such, Applicants contend that one of skill in the art would be able to make and use the invention without undue experimentation. Such is not persuasive.

As stated in the previous office action, the instant claims can be broadly interpreted as incubating any hematopoietic stem cells other than hematopoietic progenitor cells $CD34^+$ and $CD34^+CD38^-$ hematopoietic stem cells in the presence of nicotinamide or the nicotinamide analog benzamine at any concentration above 0.1mM, for any length of time, in order to expand a population of hematopoietic stem cells while inhibiting differentiation *ex vivo*. For example, Hayek et al., (WO 2005/086845, Date of publication 22-09-2005) teach a method of growing progenitor cells (p. 24, [060]) for maintenance of the undifferentiated state and/or pluripotency including using a culture medium of growth factors enriched with nicotinamide in amounts varying from about 0.5 mM to about 500 mM depending on the desired result of number of cell passages (p. 3 [008] [009] and p. 35, [104] [106]). Hence the art of record discloses critical ranges of concentration of nicotinamide, which do not include less than 0.5 mM. In relation to using any hematopoietic stem cell, the art teaches that the most critical marker used for the isolation of human blood stem cells is the sialomucin CD34 (Gallacher et al., Blood, 2000, p. 2813, col. 1). Additionally, Gallacher et al., discloses that stem cell transplantation, and expansion are designed for $CD34^+$ subsets. Moreover, Gallacher et al., teaches that some murine

stem cells that do not express detectable levels of cell surface CD34 are capable of long-term repopulation but they were devoid of short-term repopulation ability, however, human $CD34^-$ $Lin^-$ cells are unable to demonstrate hematopoietic activity *in vitro*, and it is unclear whether the human $CD34^-CD38^-Lin^-$ cells had any primitive hematopoietic function (Gallacher et al., Blood, 2000, p. 2813, col. 2).Thus the specification and art of record do not provide sufficient guidance and/ or working examples for a skilled artisan to reasonably enable the claimed invention in relation to expanding any hematopoietic stem cell population while inhibiting differentiation with any concentration of nicotinamide or benzamine, under any conditions of incubation (e.g., time).

***New rejection in response to Applicant amendment***

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 401, 411-412, 414, 416 -418, 421-425, 434, 436-438, 460 and 462 rejected under 35 U.S.C. 103(a) as being unpatentable over Brown R (US Publication No. 2002/0159984, Date of Publication October 31, 2002).

Brown R. teaches a method for *ex vivo* expansion ( e.g. proliferation) of CD34+/CD38- cells derived from cord blood (p. 1, [0010]). Brown R. discloses the presence of appropriate growth factors in the medium such as interleukins, CSF, stem cell factor, thrombopoietin (TPO), interleukin-1 (IL-I) and interleukin-6 (IL-6) which influence the rate of proliferation and the distribution of cell types in the population (p. [0049]). Moreover, Brown R. discusses that many of the cytokines can be added to the culture medium at different stages of the culture to alter the cell population including FLT3, STF, IL-I, IL-6, TPO, etc. (p. [0050]) and cytokines such as, granulocyte colony-stimulating factor (G-CSF), and granulocyte-macrophage colony stimulating factor GM-CSF) (p. 4, [0049]). Moreover, Brown R teaches that the basal medium composition of commercially available Iscove's modified Dulbecco's medium (IMDM) used for **expansion** of CD34+/CD38- cells ***ex vivo* comprises nicotinamide at concentration of 4 mg/L** (p. 3, col. 2, [0040] and p. 4, table I). Brown R. exemplifies cultures of the bone marrow CD34+ enriched population showed CD34+/CD38- cells with **significant expansion at day 3, 7 and 14**, in the absence of serum and low concentrations of IL-3, IL-6 and SCF (p. 10, [0119]), indicating expansion of the most primitive undifferentiated population of hematopoietic stem cell for use in *ex vivo* long-term engraftment. Since the source of expanded hematopoietic cell population and the incubation steps taught by Brown R. are the same as the ones set forth and claimed by the

instant invention, the ex-vivo expanded population of hematopoietic stem cells of Brown R. et al., comprises the same structural limitations as the instantly claimed population.

Brown does not specifically teach concentrations of nicotinamide of at least 0.1 mM. However, with respect to the amounts of the components in the IMDM, Brown discloses that IMDM can reformulated and "it is expected that the reformulation will contain those essential components of IMDM in amounts 0.1 to 10, preferably 0.5 to 2 times, most preferably 0.8 to 1.2 times their amounts" (p. 4, [0045]).

Brown R does not teach all the claimed nicotinamide concentrations, however, Brown R clearly recognizes that the concentration of essential components of the IMDM including nicotinamide for expansion of CD34+/CD38- cells *ex vivo* is a result effective variable depending on the desired use, e.g., maintenance, proliferation and/or differentiation of CD34+. At the time the invention was made it would have been obvious to optimize the ranges of concentration of this result effective variable, therefore the claimed invention would have been obvious.

Generally, differences in experimental parameters such as concentration will not support the patentability of the subject matter encompassed by the prior art unless there is evidence indicating such parameter is critical. . "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); ** In re

Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

### *Double Patenting*

Provisional *Rejection, Obviousness Type Double Patenting-No secondary Refence(s)*

Claims 411 remains provisionally rejected on the ground of nonstatutory double patenting over claim 208 of copending Application No. 10/767,064. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

Claim 208 of copending application 10/767,064 has been withdrawn but the rejection is maintained until claim 208 of copending application 10/767,064 is canceled.

## *New Grounds of Rejection*

### *Claim Rejections - 35 USC § 112- First paragraph- New Matter*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 401, 411-412, 414, 416419, 421-425, 434, 436-438, 460 and 462 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 401, 411, 412 and 462 recite the limitations "the presence of at least 0.1mM of exogenously added nicotinamide" . The specification discloses at p. 72, lines 3-7, the preferred final concentrations of nicotinamide "in the millimolar ranges. For example, within about 0.1 mM to about 20 mM, preferably within about 1 mM to about 10 mM, more preferably within about 5 mM to about 10 mM". No other teachings are disclosed of "at least 0.1mM of exogenously added nicotinamide". Thus is not clear that the Applicant was in possession of a genus of undefined of "at least 0.1mM of exogenously added nicotinamide" including any open ended numerical range at the time the application was filed.

## Conclusion

Applicant response filed on 06-25-2007 has been considered by the Examiner but is moot in view of the new grounds of the rejection, which is necessitated by the claims amendment.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding his application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

Maria Leavitt, PhD
Patent Examiner P/1633
Remsen 2B55
Phone: 571-272-1085

*/Anne Marie S. Wehbé/*
Primary Examiner, A.U. 1633